REPORT NUMBER ONE

ENVIRONMENTAL FACTORS INVOLVED IN THE DEVELOPMENT OF TOLERANCE TO BEHAVIORAL EFFECTS OF DELTA-9-TETRAHYDROCANNABINOL

Annual Progress Report
by
Marc N. Branch, Ph.D

August 1975

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
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University of Florida
Gainesville, Florida 32611

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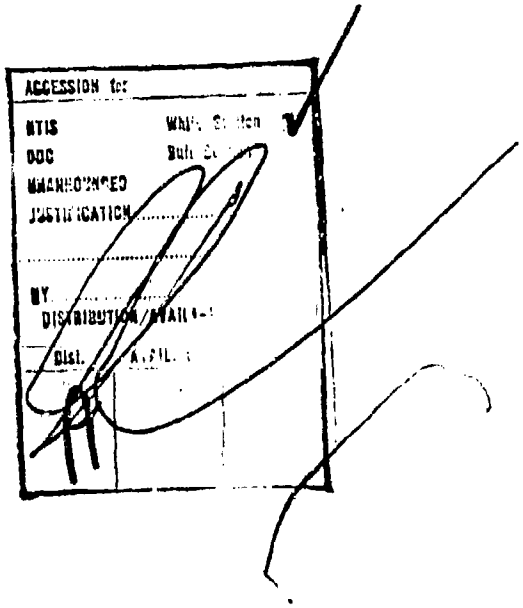
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Squirrel monkeys were trained under a variety of behavioral procedures, and then Δ^9-tetrahydrocannabinol was administered daily until tolerance developed. The aim of these experiments is to examine the interaction between behavioral procedures and the development of tolerance to behavioral effects of Δ^9-tetrahydrocannabinol. Three classes of experiments are being performed. The first group of experiments examines the roles of behavioral "cost" and baseline response rates as determinants

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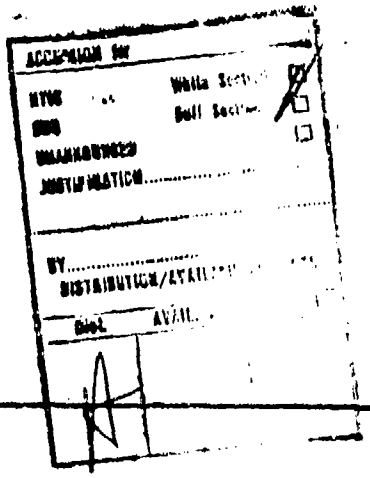
of tolerance development. Two complementary experiments in which either high or low rates are compared with moderate response rates are being conducted. In both cases administration of Δ^9-tetrahydrocannabinol results in relatively less loss of reinforcement under conditions where moderate rates prevail than where either the high or low rates prevail. Preliminary results suggest that tolerance develops most rapidly where response rate is low and behavioral "cost" is high. In the third experiment in this group adequate behavioral control is still being developed.

The second group of experiments deals with task complexity. Two experiments comprise this group. One experiment is aimed at examining the interaction of chronic administration of the drug and delay in a memory-type task (delayed matching-to-sample), but adequate behavioral control has not been achieved. The other experiment examines the interaction of repeated drug administration with the length of a complex response sequence. Testing with the shortest sequence has been completed, and overall rate of output of behavior took longer to recover from repeated drug administration than did accuracy of performance.

The last experiment compares tolerance development across different motivations. Equivalent performances have been established under three different motivational sets.



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FOREWORD

In conducting the research described in this report, the investigator adhered to the "Guide for Laboratory Animal Facilities and Care", as promulg ted by the Committee on the Guide for Laboratory Animal Facilities and Care of the Institute of Laboratory Animal Resources, National Academy of Science-National Research Council.

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INTRODUCTION AND BACKGROUND

This project consists of a series of experiments aimed at determining both quantitative and qualitative aspects of the environment that affect the development of tolerance to behavioral effects of Δ^9-tetrahydrocannabinol (Δ^9-THC), a compound that appears to be the major active constituent of marijuana (Mechoulam et al., 1970). The experiments, conducted with animal subjects, are concerned with variables that determine the degree of tolerance observed, and, in those situations where tolerance does develop, with variables that influence the rate at which the tolerance occurs.

Specifically, three general questions are being addressed. One set of experiments is directed at a determination of how schedules of food presentation for simple motor responses act as determinants of the rate at which tolerance to behavioral effects of Δ^9-THC develops. Schedules of food presentation have been shown to be powerful determinants of the degree of tolerance that is observed when amphetamine is administered chronically (Schuster et al., 1966). Two types of experiments are being conducted in this part of the project. One type compares the development of tolerance under procedures where the subject's response rate directly determines the frequency of food presentation to the development of tolerance under conditions where the frequency of food delivery is nearly independent of the subject's response rate. The other type of experiment involves procedures in which frequency of food delivery and rate of responding are controlled independently. This allows a clear assessment of the role of these two variables.

A second set of experiments systematically investigates the role of response "complexity" in the development of tolerance to behavioral effects of Δ^9-THC. In these experiments the "difficulty" or "complexity" of a task is systematically varied, and the effects of Δ^9-THC examined.

The third set of experiments investigates the role of the type of consequent events that maintains a simple motor response. Behavioral consequences that are considered both positive (e.g., food for a food-deprived animal) and negative (e.g., electric shock) will be used to maintain similar rates and temporal patterns of responding, and these baselines will be used to study the effects of Δ^9-THC.

I. Experiments involving manipulation of type of schedule, and parameters of schedules, of food presentation.

The immediate objective of this group of experiments is to determine how the type of schedule of food presentation, as well as the parameters of such schedules, can modulate the rate at which tolerance develops.

The effects of acute administration of Δ^9-THC on behavior controlled by schedules of food or water presentation have been studied by many investigators (e.g., Black et al., 1970: Boyd et al., 1963; Carlini, 1968; Frankenheim et al., 1971; Ferraro et al., 1971), and the usual finding is that Δ^9-THC reduces response rates under most schedules. There are, however, reports of rate increases under some schedules (e.g., Ferraro and Grisham, 1972; Conrad et al., 1972; Manning, 1973). Other data also indicate that the acute effects of Δ^9-THC can differ, depending on the schedule of food presentation that maintains the behavior (e.g., Ferraro et al., 1972), and also depending on the behavioral history of the animal (e.g., Drew and Miller, 1973).

Some data also suggest that the rate at which tolerance to Δ^9-THC develops varies under different schedules of food presentation. For example, McMillan et al. (1970) reported that acute administration of 1.8 mg/kg Δ^9-THC to pigeons reduced rates of pecking under a procedure in which, in the presence of one set of stimuli, every 30th peck produced access to food (a fixed-ratio 30 schedule), and in the presence of a second set of stimuli, the first peck after five minutes had passed produced access to food (a fixed-interval 5-min schedule). Under a chronic dosing regimen the key-pecking rates rose to control values, with a suggestion that key pecking under the fixed-ratio schedule recovered more rapidly. In subsequent reports (McMillan et al., 1971, 1972) such a difference was not directly reported by these investigators, but in these reports the data reported are averages for a number of subjects so it is difficult to determine whether the difference is reliably obtained. In a more dramatic demonstration, Harris et al. (1972) showed that whether or not tolerance to the rate-decreasing effects of Δ^9-THC developed at all depended on the schedule of food presentation in effect. These investigators employed rhesus monkeys in a task where presses on a lever produced food according to either a fixed-ratio 30-response schedule, or according to a schedule that required that presses be spaced by a least 15 seconds. Each schedule was correlated with a distinctive stimulus. Lever pressing under the schedule that required spaced responding showed tolerance to Δ^9-THC whereas pressing under the fixed-ratio schedule did not. These experiments show that the rate at which tolerance develops to the behavioral effects of Δ^9-THC can depend on the schedule of food presentation that maintains a simple manipulative response.

In the present project two complementary experiments examine the role of control of frequency of food presentation by an animal as a determinant of tolerance development. In the first experiment the effects of chronic administration of Δ^9-THC on behavior maintained by a schedule that produces a high response rate and also allows the animal to directly control the frequency of food delivery is compared to the effects of chronic administration on behavior under a schedule that controls a slightly lower rate but which has an identical frequency of food presentation. Specifically, behavior under a schedule according to which food is presented dependent on a variable number of responses being emitted (a variable-ratio schedule) is compared to behavior under a schedule that provides the same temporal distribution of food presentation but which doesn't require a specified number of responses for each food delivery (a variable-interval schedule). When the temporal distribution of food presentation is equal under variable-interval and variable-ratio schedules, the rate of responding is usually higher under the variable-ratio schedule (Ferster and Skinner, 1975; Zuriff, 1970). In the present experiments, however, the differences in response rate are small.

In the second experiment, the schedule that allows the animal to control the frequency of food delivery is also a schedule that produces a low response rate. Specifically, a procedure where delivery of food depends on the animal spacing its responses (a differential-reinforcement-of-low-rate, or DRL, schedule) is alternated with a procedure in which the temporal distribution of food presentation is about the same as that under the DRL schedule, but no spacing of responses is required (a variable-interval schedule). In this experiment the schedule that allows the animal to directly control the frequency of food delivery produces a much lower rate

than the schedule under which the frequency of food delivery is more independent.

A tentative hypothesis about the final outcome of these two experiments that is consistent with the literature is that tolerance should develop most rapidly under procedures where a low rate prevails and where the animal has a high degree of control over the frequency of food delivery. Conversely, tolerance should develop most slowly under conditions where a high rate prevails, and the animal has relatively little control over the frequency and distribution of food presentation.

This proposed interaction of rate of responding and degree of control by the animal over the frequency of food delivery is examined further in another experiment. In this experiment, procedures that allow response rate to be controlled independently of frequency of food delivery are employed. Three different response rates, high, medium, and low, have been generated, all of which lead to the same frequency of food presentation. The rates have been engendered using procedures similar to those employed by Blackman (1968), and each rate occurs in the presence of a specific stimulus. The effects of chronic administration of Δ^9-THC on these behaviors allows direct assessment of the influence of baseline response rate on the development of tolerance to the behavioral effects of Δ^9-THC. This procedure is also one that can lead to differential reductions in frequency of food presentation as a function of drug administration. For example, if the initial effect of the drug is to decrease responserates, then food presentation is reduced most when high rates are required and least when low rates are required. This experiment, then, also allows a test of the importance of degree of reduction in frequency of food presentation as a determinant of tolerance to Δ^9-THC.

II. Response "difficulty" as a determinant of tolerance to behavioral effects of Δ^9-THC.

Although tolerance seems a reliable outcome when simple motor responses are maintained by schedules of positive reinforcement (e.g., Carlini, 1968; Ferraro and Grisham, 1972; McMillan et al., 1970; McMillan et al., 1972), it has been reported that tolerance does not develop as readily when more "complex" tasks are used. Ferraro and Grilly (1973) recently reported a failure to observe tolerance to the accuracy-reducing effects of Δ^9-THC in a delayed matching task. In this experiment chimpanzees could produce food by identifying a stimulus that matched one shown 20 seconds previously. Repeated administration, for 42 consecutive days, of a dose of Δ^9-THC that reduced accuracy did not result in tolerance development. In a more recent report (Ferraro and Grilly, 1974), Ferraro and his colleagues have shown that some tolerance is eventually observed under this procedure. A related finding was presented by Elsmore (1972) who trained monkeys in a two-choice discrimination task. Elsmore's monkeys initiated trials in which either the duration of a light (Experiment I) or the frequency of clicks (Experiment II) served as the discriminative stimulus for pressing one of two levers. He reported that tolerance to the suppressive effects of Δ^9-THC on rate of trial initiation developed more rapidly than did tolerance to the accuracy reducing effects of the drug. These two experiments show that the type of behavioral measure employed (i.e., a rate measure versus an accuracy measure) can determine the degree of tolerance observed, and also suggest that task difficulty might be a factor determining whether tolerance is observed.

Two experiments are being conducted to determine if task "difficulty" (i.e., the degree to which responding can be brought under stimulus control) modulates the rate at which tolerance develops. The first experiment examines how the required length of a sequence affects tolerance development. Briefly summarized, this experiment involves extending a behavioral sequence (in steps) from two to five responses and determining the rate at which tolerance develops for each level of complexity. Reported here are data from experiments where the sequence is two responses long.

The second experiment employs a procedure similar to the one used by Ferraro and Grilly (1973). Animals are able to obtain food by correctly identifying a stimulus that matches one shown previously. By varying the delay between presentation of the stimulus to be matched (the sample stimulus) and presentation of the set of stimuli from which a matching stimulus is to be selected, the accuracy of responding can be continuously varied (Blough, 1959; Berryman et al., 1963). In the current project the effects of chronic administration of Δ^9-THC have yet to be examined because of difficulty in obtained good stimulus control of performance.

III. Role of the type of event maintaining behavior in the development of tolerance to the behavioral effects of Δ^9-THC.

Although it has been persuasively argued that the acute effects of many pharmacologic agents on behavior depend more on the rate and temporal pattern of responding than on the event maintaining the behavior (Kelleher and Morse, 1968), recent data (McKearney, 1974) show that when patterns and rates of lever pressing by squirrel monkeys are similar under schedules of shock presentation and under schedules of food presentation, differential effects of both morphine and chlorpromazine are observed. Given these kinds of differential acute effects there is a strong possibility that differential effects will be obtained under chronic regimens.

As mentioned above, the literature on the development of tolerance to the behavioral effects of Δ^9-THC contains many instances of tolerance observed when simple responses are maintained by schedules of positive reinforcement. On the other hand, when procedures that employ "unlearned" (elicited) behavior are used, and when procedures in which behavior is maintained by avoidance of electric shock are used, it is often the case that tolerance is not observed (e.g., Orsinger and Fulginiti, 1970; Barry and Kubena, 1971).

In the present project an experiment is being performed in which similar rates and temporal patterns of lever pressing are maintained by three different types of events; food presentation, termination of a stimulus associated with the periodic delivery of electric shock (cf. Kelleher and Morse, 1964), and presentation of electric shock (cf. McKearney, 1968). The maintenance of responding by termination of a stimulus associated with the periodic delivery of shock (a shock-stimulus complex) can be classified as an avoidance procedure (Kelleher and Morse, 1964), and some have suggested that responding maintained by electric shock presentation (schedules of response-produced shock) is in some sense elicited (Hutchinson et al., 1971). A tentative hypothesis, then, regarding the outcome of chronic administration of Δ^9-THC, is that tolerance will develop most rapidly under the schedule of food presentation, less rapidly under the schedule of termination of a shock-stimulus complex, and least rapidly, or perhaps not at all, under the schedule of shock presentation.

GENERAL METHODS

Squirrel monkeys (Saimiri Sciureus) are used in all procedures. All animals are maintained at 85% of their free-feeding weights, and they are housed in individual cages.

During experiments the squirrel monkeys work in restraining chairs that are housed in sound attenuating enclosures. The restraining chairs are equipped with levers, response keys, feeders, tail stocks and stimulus lights as needed. Sessions are monitored and controlled by a PDP-8 computer utilizating the SKED process control system.

The Δ^9-THC in these experiments is suspended in a 10% (v/v) solution of Tween 80 in 0.9% sodium chloride solution. The drug is administered intramuscularly, in a volume of 0.25ml/kg body weight, one hour prior to a session..The long pretreatment time used since earlier reports of experiments with squirrel monkeys (Scheckel et al., 1968) show a very slow onset of action of Δ^9-THC. Administrations of the vehicle alone were examined.

In order to enhance the comparability of the data from the wide range of experiments outlined here, chronic regimens are the same under all sets of behavioral parameters. Specifically, Δ^9-THC is given once per day for twenty consecutive days, or until the behavior examined returns to control levels, whichever comes first.

In those experiments in which food is used to maintain responding, monkeys are able to produce 190 mg banana-flavored food pellets. Sessions are conducted daily, seven days a week, and sessions generally last from 40 to 90 minutes, depending on the procedure.

In many of the experiments multiple schedules (Ferster and Skinner, 1957) are used. Multiple schedules consist of at least two schedules of reinforcement, and each schedule is associated with a different stimulus. The use of multiple schedules allows investigation of more than one schedule at a time in a single animal.

The Δ^9-THC is stored in refregerated darkness, and is safeguarded according to guidelines suggested by the Bureau of Narcotics and Dangerous Drugs in accord with the Comprehensive Drug Abuse Prevention and Control Act of 1970. The principal investigator is licensed by the Drug Enforcement Agency (License No. PB0108820) to obtain and use Δ^9-THC.

SPECIFIC EXPERIMENTS

I. MODULATION OF THE DEVELOPMENT OF TOLERANCE TO BEHAVIORAL EFFECTS OF Δ^9-THC BY RATE OF RESPONDING AND FREQUENCY OF FOOD PRESENTATION.

a. Development of tolerance under a multiple schedule in which high rates of responding are associated with equal frequencies of food presentation, but are not equally correlated with the frequency of food presentation.

The monkeys were trained to press a lever that produces food pellets according to a schedule under which the delivery of food depends on the number of presses, and the number of presses required varies for each pellet presentation (a variable-ratio schedule). This schedule engenders

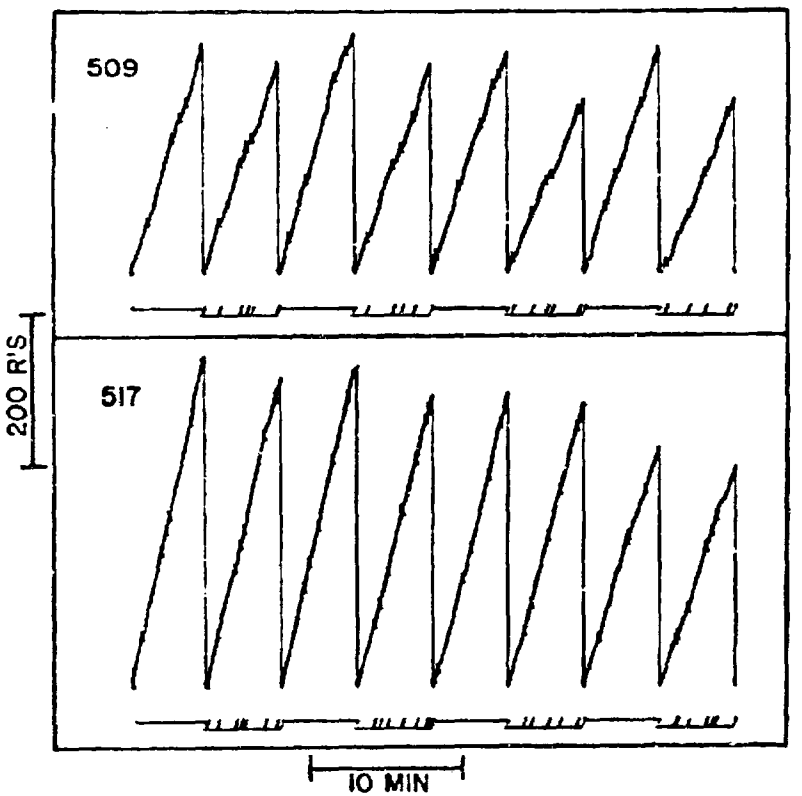

Fig. 1. Cumulative response records of lever pressing by Monkeys 509 and 517. Ordinate: cumulative presses. Abscissa: time. The event marker along the bottom is deflected downward during times when the variable-interval schedule is in effect, and upwards strokes of this pen while it is deflected occur when pellets are delivered. The small diagonal marks on the records also indicate when food pellets were delivered. The pen resets to the baseline at the end of each five-minute component.

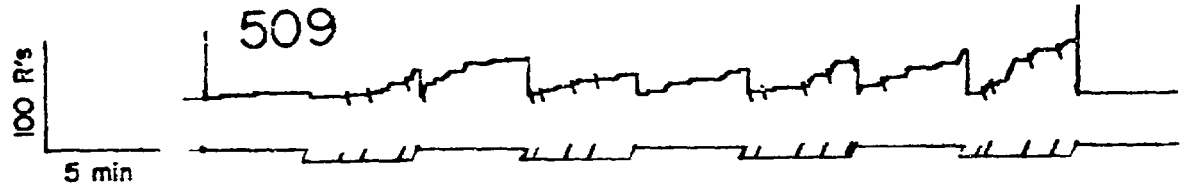

Fig. 2. Cumulative response record from the first session in 1.0 mg/kg of Δ^9-THC was given to Monkey 509. See Fig. 1 for details.

high, constant response rates. When lever pressing was well established under this schedule, which allows the animal to directly control the temporal frequency of food delivery, a multiple schedule was instituted. In the presence of one stimulus (white pilot lights) a variable-ratio 74 schedule is in effect. In the presence of a second stimulus (blue pilot lights) a schedule is put into effect that allows lever presses to produce food pellets with approximately the same frequency and distribution as during the variable-ratio schedule, but that requires only that a single response be made after the schedule has arranged that a pellet is available (a variable-interval schedule). This schedule also produces high rates of responding. Figure 1 shows cumulative response records from the two monkeys currently serving in this experiment. Each schedule and its associated stimulus (i.e., each component of the multiple schedule) is in effect for alternate five-minute periods throughout a session. The intervals in the variable-interval schedule are determined by using the inter-pellet intervals observed during the variable-ratio schedule. That is, the times between pellet deliveries under the variable-ratio schedule are recorded, and a variable-interval schedule that is comprised of the average of these inter-pellet intervals is employed. Thus, the variable-interval schedule is "yoked" to the variable-ratio schedule. A new variable-interval schedule was constructed every seven to fourteen sessions until performance under the variable-ratio schedule was stable enough so that there were negligible changes in the variable-interval schedule.

Although the response rates during the variable-ratio and variable-interval schedules are quite similar it is not the case that the monkeys cannot discriminate the white from the blue lights. Three test sessions during which no pellets were delivered during the blue lights resulted in a marked reduction in rate of lever pressing during that component, while rates in the other component remained high.

Monkey 509 was the first to receive Δ^9-THC. He received 1.0 mg/kg of the drug for 20 consecutive sessions, followed by 53 days without drug. After the 53-day period, the same dose was again administered for 20 consecutive days to see if the original effects could be reproduced.

A cumulative response record from the first session under 1.0 mg/kg Δ^9-THC is shown in Figure 2. The drug produced an overall decrease in response rate in both components. The decrease was roughly uniform throughout the session. Figure 3 displays quantitative data from both the chronic series' of administration. The figure shows that prior to both series an approxima equal number of pellets was being earned in each schedule, and that the response rate during the variable-ratio schedule was consistently higher than the rate during the variable-interval schedule. Over the course of both 20-day series of drug administration tolerance developed to the depressive effects of the drug in both components of the multiple schedule, and tolerance appeared to develop at the same rate under both schedules. Also of interest in the fact that during drug sessions there were no consistent differences in response rates between the two components. When administration of the drug was discontinued (injections of the vehicle continued) after the first 20-day phase of chronic administration, response rates gradually decreased for about 10 sessions and then increased toward control levels. Control levels of responding were recaptured 30 days after the last dose of Δ^9-THC. When drug administrations were halted after the second 20-day chronic series, rates immediately dropped, and at the time

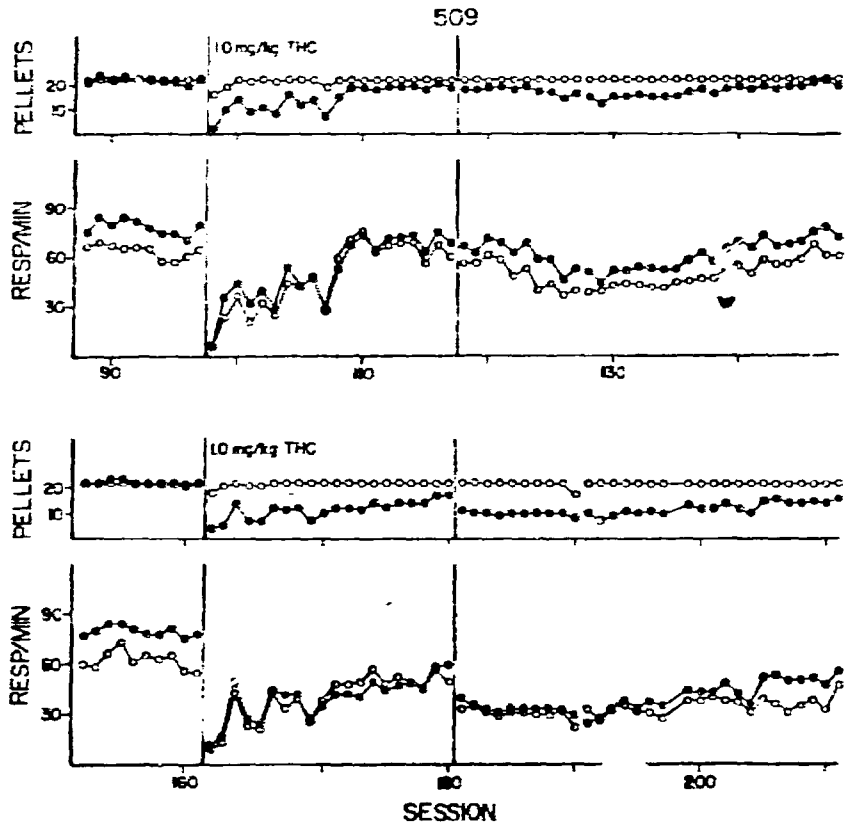

Fig. 3. Rates of lever pressing and frequency of food pellet presentation (pellets per session) over sessions for Monkey 509. The top pair of figures show data from control sessions, 20 sessions under a daily drug regimen (1.0 mg/kg/day), and 10 sessions (sessions 118 to 127) that were preceded by administration of the drug vehicle. The lower pair of graphs show data from the second series of daily pre-session administrations of the drug. Open circles are data from the variable-interval schedule, and filled circles are data from the variable-ratio schedule.

of this writing (42 days have passed) control levels of responding have not been recaptured.

Monkey 517 was also exposed to 20 days of daily administration of 1.0 mg/kg of Δ^9-THC. Data from this monkey are shown in Figure 4. At the end of the phase it was discovered that Monkey 517 had a severely abcessed molar, so it is not possible to tell whether the decline in rates observed during the last 12 sessions of drug administration were due to the drug or to the abcess.

b. Development of tolerance under a multiple schedule in which low and moderate rates are associated with equal frequencies of food delivery.

The animals were first trained to respond (press a lever) under a schedule where presentation of food depended on responses being spaced by some minimum amount of time (a differential-reinforcement-of-low-rate, or DRL, schedule). This schedule resulted in a low rate, and a significant proportion of the interresponse times (times between two lever presses) were slightly longer than the minimum (28 sec) required for food presentation. When behavior stabilized under this procedure, a multiple schedule was put into effect. One component of the multiple schedule is the DRL schedule, and the other component is a variable-interval schedule, and the components alternate every 5 minutes. As in the experiments with the variable-ratio schedule, the distribution of interpellet intervals during the DRL schedule is recorded each session. The variable interval schedule is constructed with a distribution of intervals that approximates the distribution of interpellet times during the previous DRL component. So, again, the variable-interval schedule is "yoked" to the schedule in the other component of the multiple schedule. The two components of the multiple schedule control quite different performances. Figure 5 shows cumulative response records of pressing by the two monkeys currently in the experiment. The variable-interval schedule controls a rate of pressing from five to ten times higher than the rate controlled by the DRL schedule. The DRL schedule also exerts control over the spacing of lever presses while it is in effect.

Both of the monkeys in this experiment have been exposed to chronic administration of 0.25 mg/kg of Δ^9-THC, but Monkey 504 developed a serious leg infection during the chronic administration phase that made data from the last part of the chronic series uninterpretable.

Cumulative response records from the first day on which responding occurred during the series of chronic administrations (third session for Monkey 501 and first session for Monkey 504) are shown in Figure 6. Response rates during the DRL schedule were elevated for both monkeys, whereas rates under the variable-interval schedule were increased for Monkey 501 and decreased for Monkey 504. Daily response rates of Monkey 501 are plotted in Figure 7. The first two administrations of 0.25 mg/kg of Δ^9-THC completely suppressed lever pressing by this monkey, and then in the third session response rates under both schedules were increased. The rates under both schedules remained elevated above control levels throughout the 20 days of drug administration.

Figure 8 shows relative frequency distributions of interresponse times (IRT's) during the DRL schedule for both monkeys. The distributions from control performance (filled triangles) show that most interresponse times were 28 sec or longer under initial non-drug conditions. The initial effect

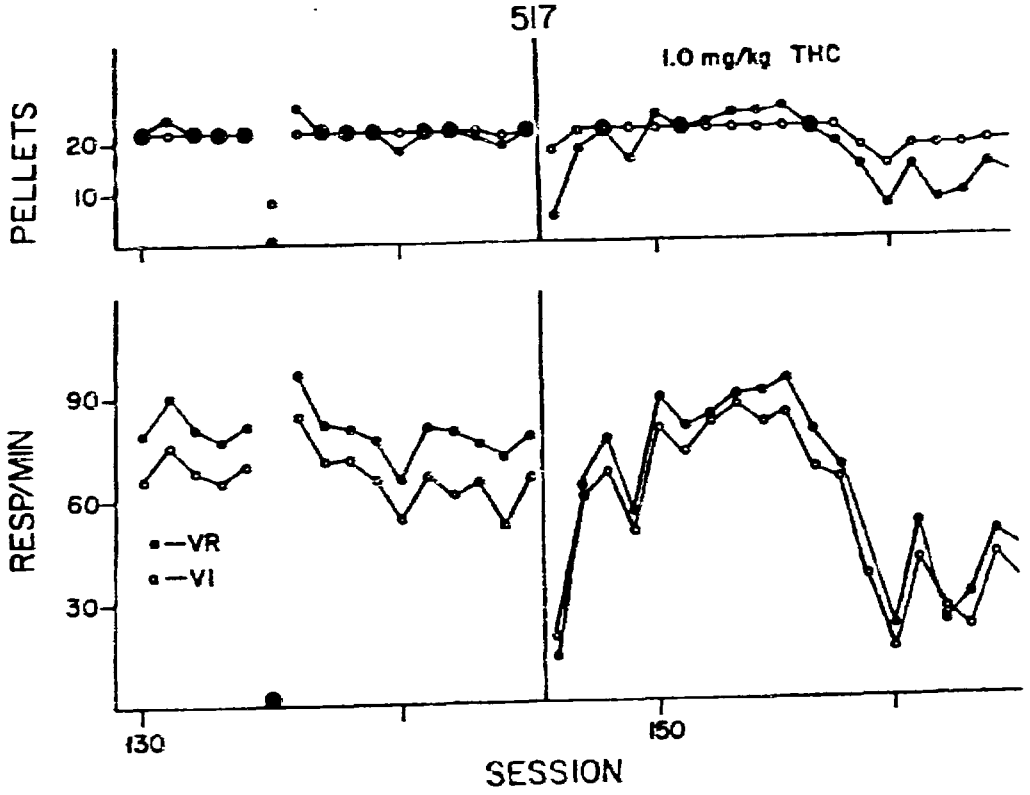

Fig. 4. Rates of lever pressing and frequency of food pellet presentation (pellets per session) over sessions for Monkey 517. Open circles depict data from the variable-interval schedule and filled circles depict data from the variable ratio schedule. 1.0 mg/kg of Δ^9-THC was administered prior to session 135 and prior to sessions 146 through 165.

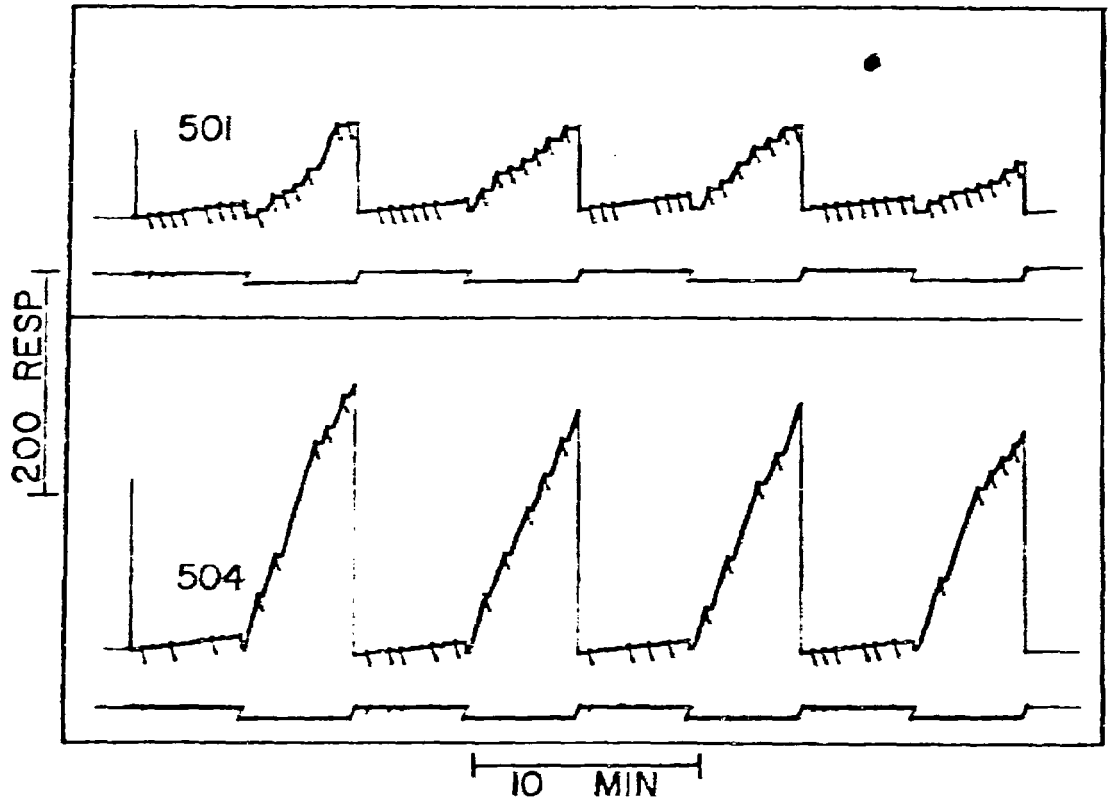

Fig. 5. Cumulative response records of lever pressing by Monkeys 501 and 504. Ordinate: cumulative presses. Abscissa: time. The event marker along the bottom is deflected downwards during five-minute periods when the variable-interval schedule is in effect. Small diagonal marks on the records indicate food pellet deliveries. The pen resets to the baseline at the end of each five-minute component.

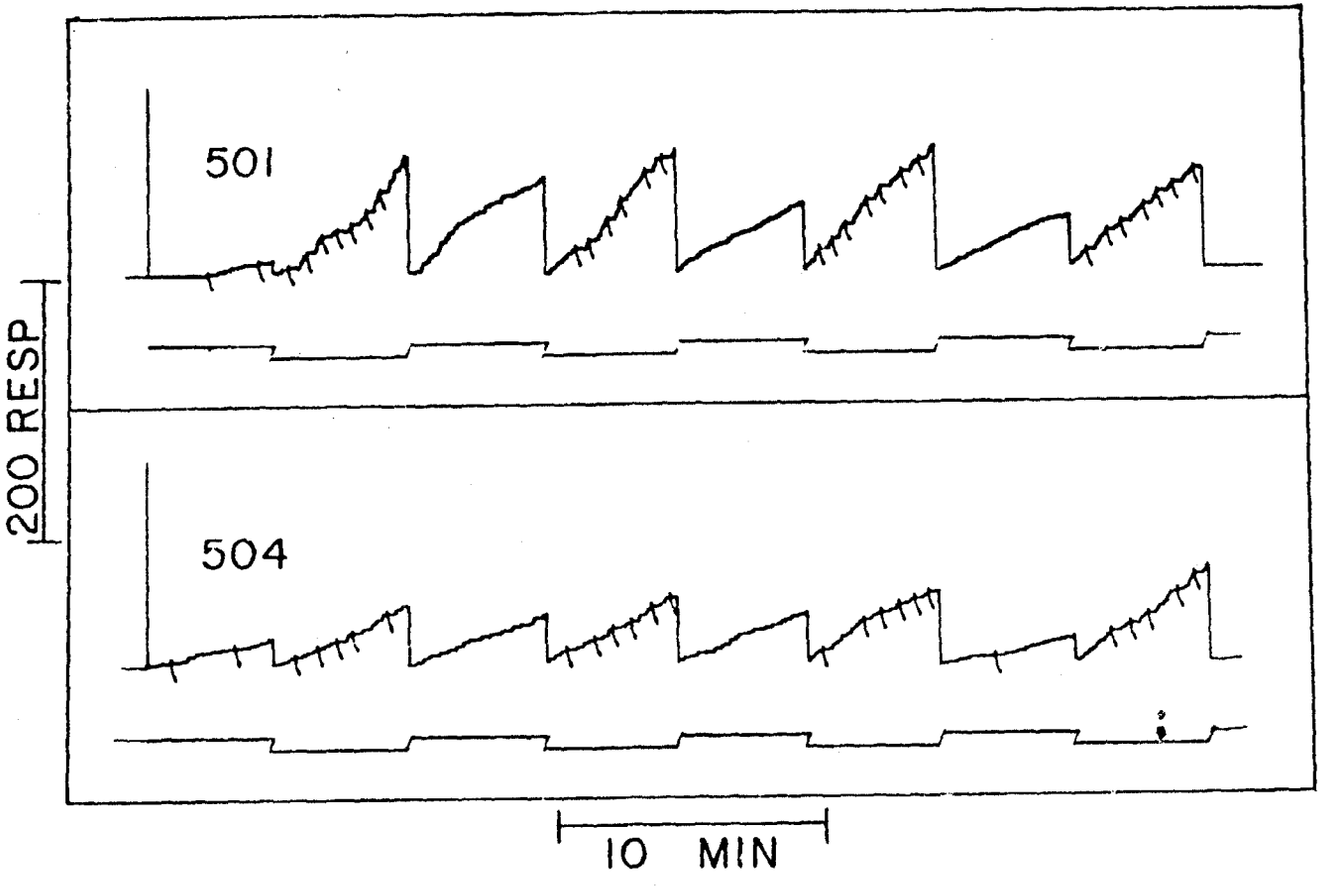

Fig. 6. Cumulative response records of performance by Monkeys 501 and 504 during the first session in which responding occurred when 0.25 mg/kg of Δ^9-THC was administered prior to the session. Details of the records are the same as in Figure 5.

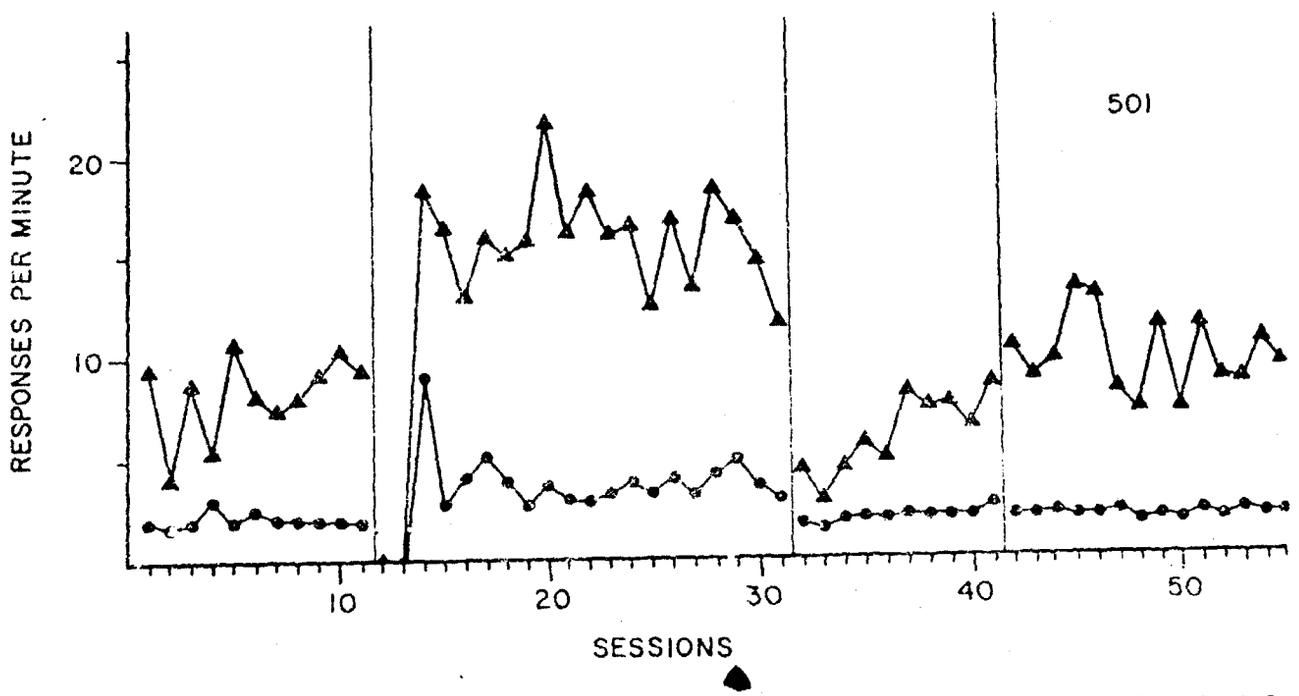

Fig. 7. Daily response rates of subject 501 under the multiple DRL, variable-interval schedule during baseline, chronic administration of 0.25 mg/kg of Δ^9-THC (12th through 31st session), vehicle control (32nd through 41st session), and control sessions. Triangles represent rates during the variable interval schedule and circles represent rates during the DRL schedule.

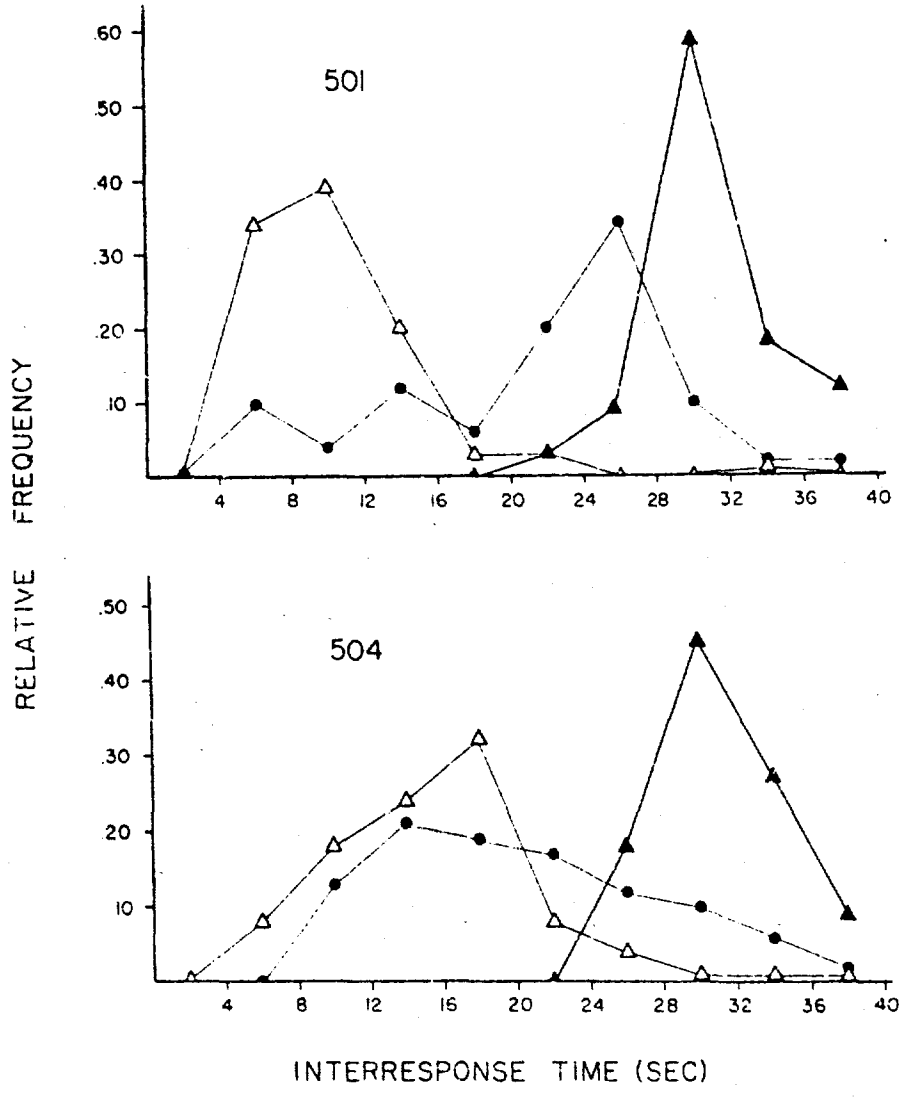

Fig. 8. Relative frequency of interresponse times for Monkeys 501 and 504. The filled triangles show data from a control session, the open triangles show data from the first session of administration of Δ^9-THC for Monkey 504 and from the third session of drug administration for Monkey 501. The filled circles show data after a few sessions of daily drug administration. See text for further details.

of the drug (open triangles) was to shift the distribution to the left without greatly increasing the dispersion of values. Continued administration of the drug resulted in a flattening of the distribution, that was followed by the appearance of a distribution similar in form to that seen under control conditions except that the mode of the distribution was at a value less than 28 sec. This is displayed in Figure 9 where the filled triangles show the IRT distribution for Monkey 501 on the last day that the drug was administered. Also illustrated in Figure 9 is the distribution from the first session after the 20 consecutive sessions of drug administration. A large proportion of the IRT's were 36 sec or longer. Eventually, however, behavior under the DRL schedule recovered to its original state as illustrated by the filled circles.

c. Tolerance development under a multiple schedule in which unequal response rates are associated with equal frequencies of response-dependent food presentation.

The monkeys which serve in these experiments were trained to press a lever under a multiple schedule that has three components. Each component is associated with a variable-interval schedule with a mean value of 90 sec. In one component, signalled by one color (white), food pellets are delivered according to the variable-interval schedule only following three interresponse times (i.e., times between two presses, IRT) of less than 0.50 sec. Specifically, when the variable-interval schedule arranges that a food pellet is available, the third interresponse time of less than 0.5 sec results in the delivery of the pellet and resumption of timing by the variable-interval schedule. The response rate is highest in this component. In the second component, signalled by green light, pellets were delivered according to the variable-interval schedule only following interresponse times between 1.5 and 2.5 sec, and this arrangement produces a moderate rate of responding. In the third component, food is presented according to the variable-interval schedule only after inter-response times longer than 8 sec, and a low rate prevails during this component. Components last 30 minutes each and are presented once each session. This procedure resulted in good control of the behavior of Monkey 505, and less than desirable control in Monkey 513. Figure 10 shows cumulative response records from both monkeys. As the records show, Monkey 505 emits three clearly distinguishable response rates, whereas Monkey 513 emits only two clearly distinguishable rates, the rates in the two components designed to control moderate and low rates being nearly equal. Monkey 513's behavior in the component requiring the low rate has not been well controlled for over five months in spite of several minupulations designed to instill a low rate. When poor control first appeared (initially, good control of a low rate was obtained in this monkey), the requirements in the component that is supposed to control a low rate were altered so that two consecutive IRT's of greater than 8 sec were required in order for a pellet to be delivered once arranged by the variable-interval schedule. This resulted in a considerable reduction in the number of pellets obtained in the low-rate component by Monkey 513 (from about 20 per session to about 4 per session), but the monkey's response rate did not change over the next 40 sessions. Next it was arranged that, for Monkey 513, no pellets were delivered in the presence of the blue lights that signal the low-rate condition, and this procedure was kept in effect for 31 sessions. Over the course of these sessions, the response rate in the presence of the blue lights dropped from about 20 per min to about 2 per min. However, as soon as pellets were again delivered, even though two consecutive

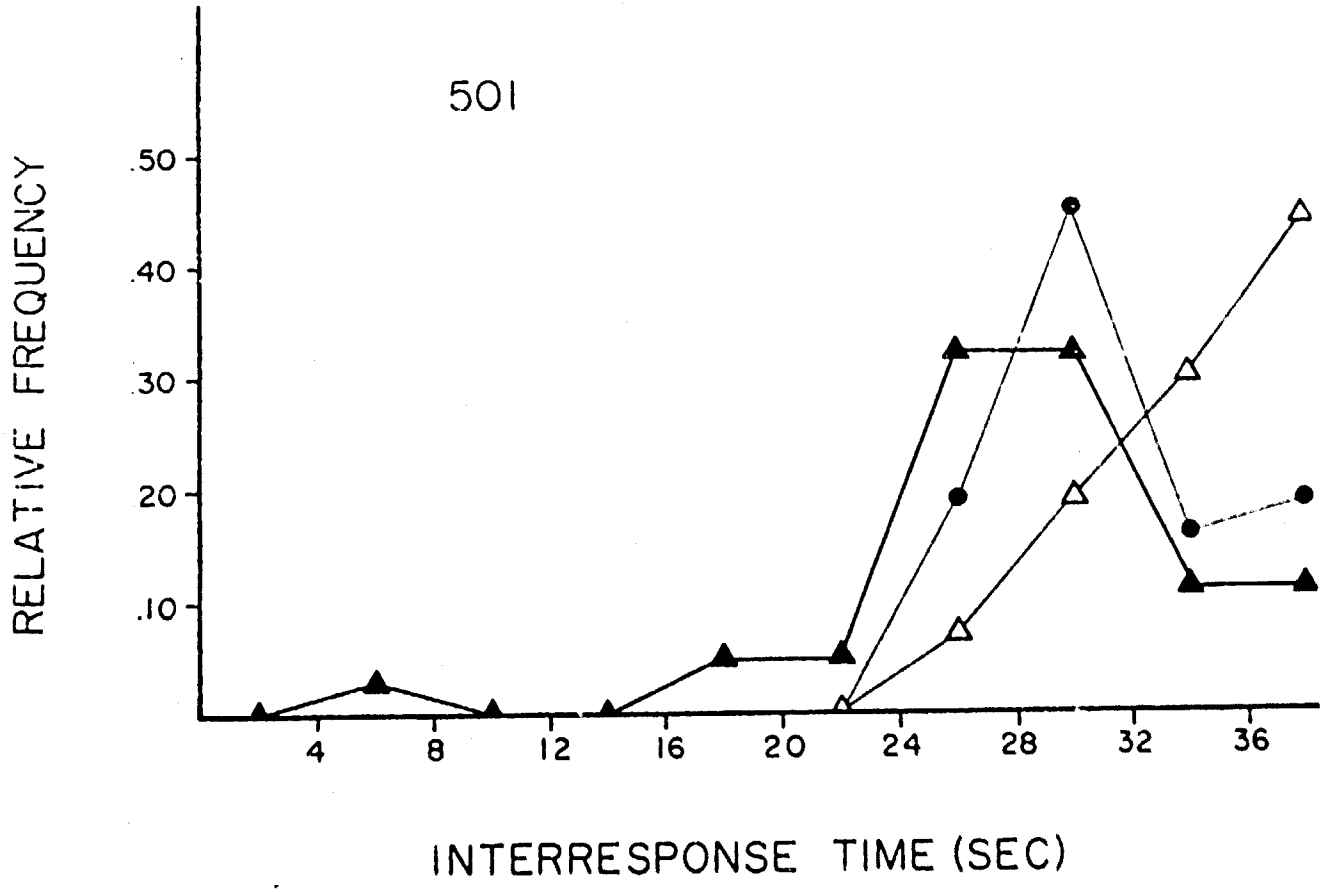

Fig. 9. Relative frequency of interresponse times from the 20th session under daily administration of Δ^9-THC (filled triangles), the first session after drug administration was discontinued (open triangles), and from a later control session (filled circles) for Monkey 501.

IRT's of longer than 8 sec were required, the response rate immediately rose to about 20 presses per min and only about five pellets per session were obtained in the low-rate component (as compared to about 20 pellets per session in each of the other two components).

During this time Monkey 505's lever pressing continued to be well controlled, so a series of administrations of 1.0 mg/kg of Δ^9-THC was begun. For the first four days Monkey 505 did not press the lever, and then on the fifth day pressed the lever a few times during the high-rate component. On the sixth day of drug administration, responding returned in all three components. Tolerance seemed to be developing at approximately equal speeds in all three components. After 18 days, however, the monkey was removed from the experiment for 19 days because of a tooth abcess. During the 19 days 1.0 mg/kg of Δ^9-THC was administered daily. After the monkey was returned to the experiment, daily dosing continued for another 40 days. By the end of the 40 days performance had completely recovered in the components requiring high and moderate rates, but the proportion of IRT's exceeding 8 sec in the component requiring a low rate did not return to control levels. Thus drug administration resulted in an apparently permanent reduction in the number of food pellets earned in the low-rate component. Discontinuation of drug administration had no large effect on any measure.

After 27 sessions after the last drug administration, the requirement in the low rate component was relaxed for both monkeys to require only a single IRT greater than 8 sec to obtain a pellet once delivery was arranged by the variable-interval schedule. It was hoped that this manipulation would result in more long IRT's being reinforced, and thus enhance the control of Monkey 513's behavior. The change, however, resulted in little change in response rates by either monkey even though it did lead to more pellets being earned in the low-rate component.

The next attempt to produce better separation of response rates consisted of the changing the IRT requirements in the component controlling the middle rate, the logic being "if you can't get the low rate down, then move the mid rate up." Instead of IRT's between 1.5 and 2.5 sec being eligible for pellet delivery IRT's between 1.0 and 2.0 sec were made eligible in the mid-rate component. This change in procedure produced no change in the behavior of Monkey 513 and resulted in a 50% increase in rate during the mid-rate component for Monkey 505.

In the most recent modification of the procedure, the order in which the components appear each session was changed. Instead of the order being high rate, moderate rate, low rate, it is currently low rate, high rate, moderate rate. At the time of this writing only five sessions of this procedure have been conducted.

II. DEPENDENCE OF TOLERANCE TO THE BEHAVIORAL EFFECTS OF Δ^9-THC ON THE "COMPLEXITY" OF THE RESPONSE REQUIREMENT.

a. Length of a response sequence as a determinant of tolerance to the disruptive effects of Δ^9-THC.

The restraining chair for this experiment is equipped with a retractable lever, five response keys that can be illuminated from behind, and a pellet dispenser. The monkeys initiate a trial by making five responses on the lever. Five presses on the lever result in retraction of the lever and in two of the keys being lighted (a different two on each trial), one by red

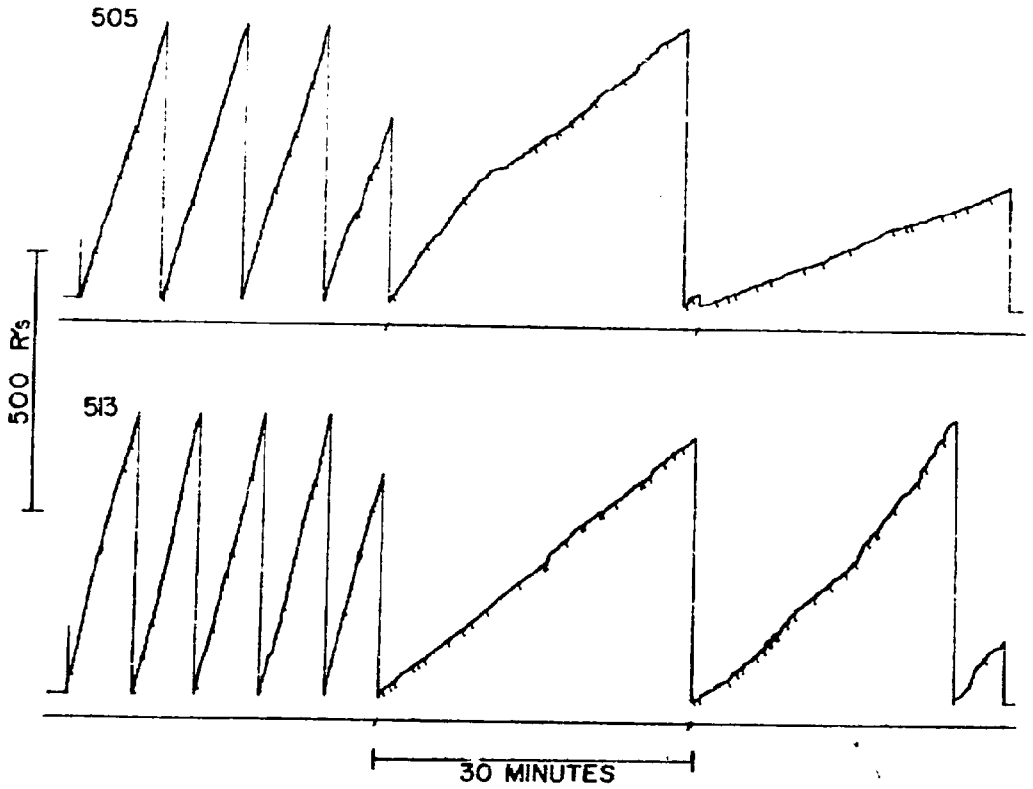

Fig. 10. Cumulative response records of lever pressing of Monkeys 505 and 513. Ordinate: cumulative lever presses. Abscissa: time. Short diagonal strokes on the record indicate the delivery of food pellets. A mark on the event record occurred at the end of a schedule component and the response pen also reset at that time.

light and another by green light. A "correct" sequence of responses consists of a press on the green key, followed by four presses on the red key. The first press on the green key darkens it. Any press on a dark key, or pressing on the red key before pressing on the green one, ends the trial and darkens the enclosure for 30 seconds. Food pellets are accompanied by 5-sec of light in the food cup and are delivered following 50% of the correct trials. The two main dependent variables in the experiment are the percentage of correct trials and the rate at which trials are initiated. Sessions last for either 80 trials or for 60 min, whichever occurs first.

During the chronic drug administration phase Monkey 510 was administered 2.0 mg/kg of Δ^9-THC daily and Monkey 511 received 1.0 mg/kg prior to each session. These doses were picked because they were the smallest dose would produce any effect at all on the behavior. Figure 11 shows the percentage of correct sequences occurring during the fifteen sessions preceeding the chronic administration phase, during the 20 sessions that were preceeded by drug administration, during 10 sessions where the vehicle was administered daily, and finally during several more sessions that were not preceeded by injections. Subject 511 made no responses the first day the drug was administered, and Monkey 510 completed only four sequences. Subsequently, recovery to high levels of accuracy occurred rapidly, although the data from Monkey 510 showed increased variability. After drug administrations were discontinued the data from Monkey 511 showed increased variability.

Figure 12 shows the rate at which trials were initiated over the same sessions shown in Figure 11. This measure includes both correct and incorrect sequences. This measure returned to baseline levels somewhat more slowly than did percent correct during the chronic drug administration phase, and when drug administrations were stopped there was a marked decrease in the rate at which trials were initiated. After the last drug administration the rate was not only low but also quite variable, and the variability persisted for quite a few sessions for Monkey 511. The sessions during which the rate was low for Monkey 511 were characterized by long periods during which no responses occurred.

Throughout all the sessions reported virtually all errors consisted of pressing the red key before pressing the green key. Any press on an unlighted key is an error, but such errors were very rare both under control and drug conditions.

When rates of trial initiation and completion were decreased most of the decrease could be attributed to the latency from the onset of a trial to the first press on the lever. That is, once a sequence was begun it proceeded rapidly under both drug and non-drug conditions.

Position preferences did not appear to be a factor. For both monkeys errors occurred with equal frequency on all five keys, and there was no systematic relation between particular red and green key configurations and accuracy. On those occasions where a correct trial is not followed by a pellet, the food cup is illuminated for 5 sec.

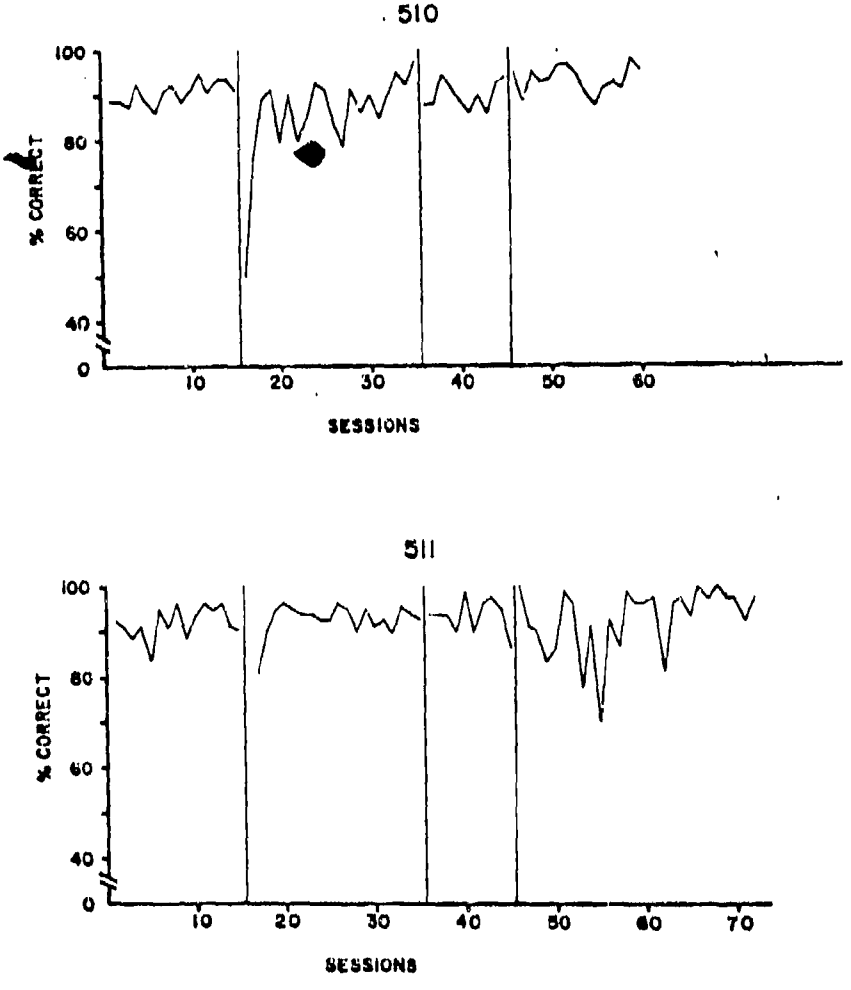

Fig. 11. Percent correct sequences over sessions for Monkeys 510 and 511. The first 15 points show data from control sessions, the next 20 data from sessions that were preceeded by injections of Δ^9-THC (2.0 mg/kg for Monkey 510 and 1.0 mg/kg for Monkey 511), the next 10 data from sessions preceeded by injections of the drug vehicle, and the remaining points show data under non-injection conditions.

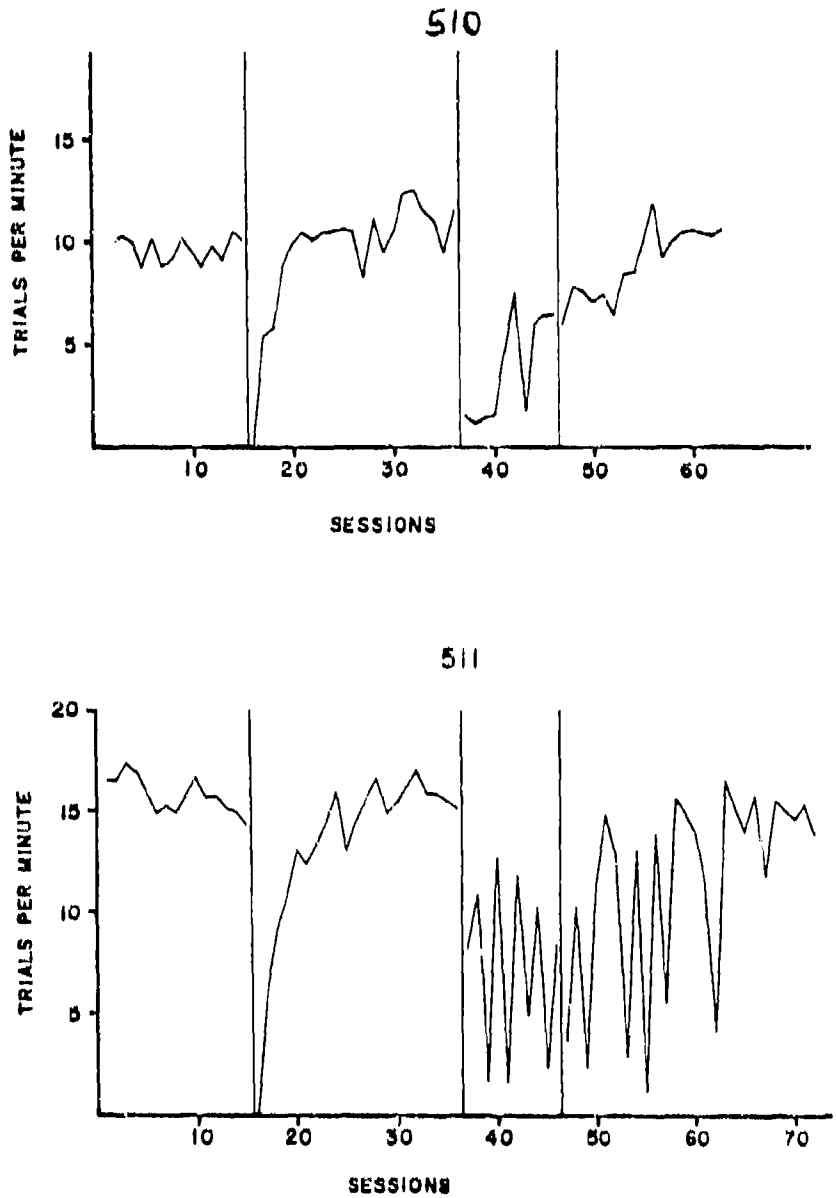

Fig. 12. Trials completed per minute for Monkeys 510 and 511 over sessions. The data displayed are from the same sessions as those shown in Fig.11.

b. Development of tolerance as a function of delay value in a delayed matching-to-sample procedure.

The purpose of this experiment is to examine the development of tolerance to Δ^9-THC under a procedure where discriminative responding is emitted at various delays after presentation of the discriminative stimuli.

On the front wall of the restraining chair is a retractable lever. Above the lever are three horizontally aligned translucent keys at approximately the monkey's eye level. The keys can be transilluminated from behind by colored lights, and at the top of the front wall is a houselight for general illumination.

The terminal procedure (matching to sample) for these monkeys will require the monkeys to press the lever four times to produce a randomly selected sample color on the center key (the lever will be retracted except during times when it is operative). Five presses of center key will turn that key dark, and, after a variable delay (during which all lights in the enclosure will be darkened) the two side keys will be lighted with different colors, one of which will match the previously presented sample color. Pressing the matching key will be counted as a correct response and will produce a food pellet following 50% of the trials. Pressing the other side key will produce a period of timeout.

After initial shaping of pressing the lever and lighted keys, the first procedure to which the monkeys were exposed in our attempt to achieve the terminal program was a matching-to-sample procedure with a zero-sec delay between termination of the sample and presentation of the side-key choices. Initially, pressing the incorrect side key had no effect. After a few sessions timeouts were made contingent on incorrect presses, after which the same trial would be repeated (correction procedure). The monkeys were exposed to this procedure for 10 days with no evidence that stimulus control was developing. For the next 35 days two presses of the correct key were required to produce a food pellet, and again no evidence of stimulus control was observed, i.e., responding on the side keys appeared to be essentially random.

Over the next 72 sessions a number of modifications of the procedure were tried in order to get behavior under stimulus control of the key colors. These changes included reducing the response requirement on the correct key to one and requiring two correct trials to produce reinforcement. The requirement for reinforcement was next raised to three correct trials, and then changed so that two consecutive correct trials (resetting fixed ratio) were required. Once again stimulus control did not develop, so the number of possible colors on the keys was lowered from three to two, but still no stimulus control was achieved. The last procedural change in this part of the experiment consisted of presenting only red on the sample key for the first half of each session and only green on the sample key for the second half of each session. In this phase only a single correct response was required. A modification of the apparatus was also made during this phase that consisted of attaching short plexiglas extensions to the recessed side keys in order to make it more likely that the "tickling" type topographies exhibited by both monkeys would be more likely to result in a press of the

keys. Following this procedure, the resetting fixed-ratio requirement was reinstated as was the random selection of sample colors on a trial. An additional change was that an increased number (10) of responses on the center key was required. After 35 days under this procedure both monkeys were responding very slowly, and there was still no evidence of stimulus control by key colors.

Next we embarked upon the procedure that is currently in effect. We are attempting to synthesize matching-to-sample performance out of its component conditional discriminations. In effect is a "go-nogo" procedure that is identical to the matching-to-sample procedure except that in the last portion of the sequence only one side key is lighted. If that key is the same color as the sample key was, then a press on the lighted key produces a food pellet. Failure to press the key within 10 sec results in a timeout and presentation of the same trial again. If the side key's color is different from the sample then not pressing the key for t sec results in presentation of a food pellet, whereas pressing the key eliminates the possibility of reinforcement for that trial, and the key remains illuminated until it has not been pressed for 10 sec. t can be varied, and at present both monkeys have t = 5 sec. Both monkeys are performing at above chance levels. The percent correct for the last 15 sessions prior to this writing ranges from 55 to 70% for one monkey and from 65 to 85% for the other. Although it appears that much of the behavior at present is under the control of the differential temporal aspects of the "go" and "nogo" portions of the procedure, it is encouraging to note that some control exists that can be manipulated. Next we will gradually eliminate the differential temporal aspects of the procedure in the hope that differential control by key color will come to predominate. When that is accomplished the matching-to-sample procedure can be reinstated.

III. DEPENDENCE OF TOLERANCE TO BEHAVIORAL EFFECTS OF Δ^9-THC ON THE TYPE OF EVENT MAINTAINING BEHAVIOR.

a. Tolerance development under a multiple schedule in which similar rates and temporal patterns of responding are maintained by three different consequential events.

The two monkeys in this experiment were first trained under a continuous avoidance schedule in the presence of two white lights. A fixed-interval 5-min schedule of 7-MA shock presentation was then added to the avoidance procedure, and finally the avoidance program was removed. Typical fixed-interval performance then developed. Next a second component was added to the schedule. At first, in the presence of blue lights, 30 lever presses were required to terminate the component by turning out the blue lights and initiating a 30-sec timeout. If the 30 presses were not completed before 35 sec elapsed then 7-mA shocks were delivered at 5-sec intervals until the 30 press was made. After six sessions under this procedure the schedule in blue was changed so that, at the end of one minute, intense electric shocks were scheduled to occur every 2 seconds. The first press on the lever after this stimulus had been on for one minute, however, terminated both the stimulus and the train of shocks. Thus, shock could be avoided entirely by making a response between one minute and one minute plus 2 seconds from the beginning of the stimulus. This is a fixed-interval 1-min schedule of termination of a shock-stimulus complex. After four sessions of exposure to the fixed-interval 1-min schedule of termination of a shock-stimulus

complex, the schedule in the presence of the blue light was changed to a fixed-interval 5-min schedule of termination of a shock-stimulus complex. Over the next 22 days each session began with a fixed-interval 5-min schedule of shock presentation, and then components alternated until 15 components (8 fixed-interval shock-presentation and 7 fixed-interval shock-stimulus-complex-termination components) had been completed. Thirty second timeouts separated components.

Finally, a third component was added to the multiple schedule; a fixed-interval 5-min schedule of food presentation. Specifically, in the presence of two green lights, the first lever press after five minutes had elapsed produced a 190-mg food pellet and light in the food cup for 5 sec, followed by 30 sec of timeout. Each session consisted of five repetitions of the sequence fixed interval 5-min shock presentation, fixed interval 5 min termination of a shock-stimulus-complex, fixed interval 5 min food presentation.

After 27 sessions under the three component multiple schedule, limited holds were added to each component that specified that if a response was not made within the sixth minute after the beginning of a component, then the event that usually terminated the component was presented independently of the subject's behavior. For example, if a monkey did not press the lever during the sixth minute of green light, then a food pellet was delivered automatically at the end of the sixth minute. A timeout then ensued, and the next component followed. Under this program Monkey 502's rate of lever pressing during the fixed-interval schedule of shock presentation was lower than its rates under the other two schedules, and Monkey 506's rate under the shock-presentation schedule was much higher than the rates under the other two components. The program was then changed so that a sequence of fixed-interval schedule of food presentation, fixed-interval schedule of shock-stimulus-complex termination, fixed-interval schedule of shock presentation was repeated five times each session. Thus, all that was changed was the order in which the components appeared. Under this program Monkey 502's rate under the food presentation schedule was lower than the rates under the other two schedules, whereas Monkey 506 continued to emit higher rates under the shock presentation schedule.

Continuing to make changes in the procedure in order to obtain equal rates in the three components, the next alteration in procedure again involved changing the sequence of schedule components. Under these conditions, which are also the current conditions, the sequence consists of five repetitions of the schedule of shock-stimulus-complex termination, followed by five repetitions of schedule of shock presentation, followed in turn by five repetitions of the schedule of food presentation. Under these conditions response rates in the three components are nearly equal. Figure 13 shows cumulative response records from both monkeys under the current conditions. Although Monkey 502's overall rates in the three components are nearly equal, the temporal patterns of responding are not. The period of not pressing at the beginning of a five minute period under the schedule of food presentation is reliably shorter than the period of not pressing under the other two schedules. For Monkey 506 the period of not responding at the beginning of shock presentation components is usually longer than the pauses in the other two components.

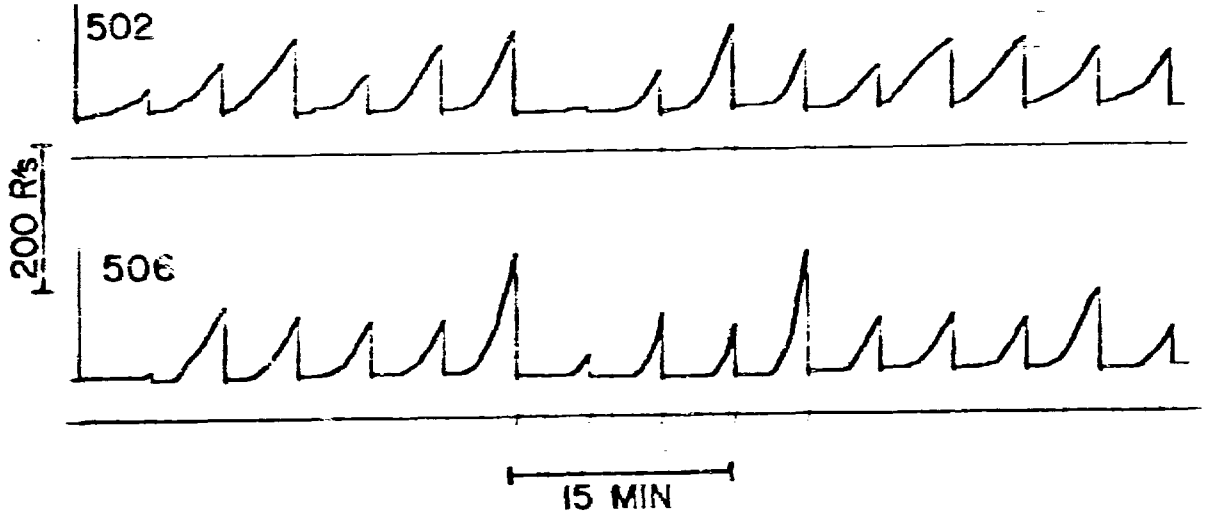

Fig. 13. Cumulative response records of lever pressing by Monkeys 502 and 506. Ordinate: cumulative lever presses. Abscissa: time. The pen reset to the baseline at the end of each fixed-interval component, and marks on the event record show where shocks were delivered. See text for further discussion

At the time of this writing, these two monkeys have just begun to be tested under chronic administration of Δ^9-THC.

CONCLUSIONS

Most of the experiments in the project are not yet finished so definitive conclusions are not warranted. Nevertheless, some statements can be made concerning the implications of the data generated to date. First, the experiment in which tolerance development was examined under variable-ratio and variable-interval schedules provided data that are not consistent with an hypothesis that tolerance to behavioral effects of Δ^9-THC is more likely to develop, or will develop more rapidly, under circumstances where the initial effect of the drug results in some "cost" to the subject. In that experiment, both variable-ratio and variable-interval response rates were reduced by 1.0 mg/kg of Δ^9-THC, and, of course, this resulted in a large reduction in frequency of pellet delivery under the variable-ratio schedule and a much smaller reduction in the frequency of food presentation under the variable-interval schedule. Nevertheless, tolerance developed at equal rates under the two different schedules. It might be argued that the monkeys' behavior was not under stimulus control (i.e., that the monkeys did not discriminate between the two schedule components) during the course of drugging, since response rates in the two components were approximately equal during sessions in which the animals were drugged. Evidence against this conclusion comes from the experiments where tolerance development under DRL and variable-interval schedules was examined. The cumulative response records in Figure show the initial effects of Δ^9-THC on the behavior in this experiment. What is important to note is that, even though behavior was disrupted, differential responding was maintained. The restraining chairs used in these two experiments are virtually identical, so the location and type of stimuli signalling the components of the multiple schedules are the same in the two experiments. Thus, it seems unlikely that the two monkeys in the experiment comparing tolerance development under variable-ratio and variable-interval schedules were rendered unable to discriminate between the stimuli signalling the two schedules. Of course, the two monkeys in this experiment were receiving a much larger dose of the drug than were the two monkeys in the experiment where performances under DRL and variable-interval were being compared, so a conclusive statement about whether or not stimulus control was disrupted in the variable-ratio experiment will depend upon further experimental analysis.

The data from Monkey 509, who was exposed to chronic administration of 1.0 mg/kg of Δ^9-THC twice, are very encouraging. The fact that the original acute effect of Δ^9-THC could be recaptured only 50 days after the last of 20 consecutive daily administrations, suggests that within-subject analyses of chronic effects of the drug are possible, thus providing, within a reasonable span of time, all the power that a within-subject experimental design can give.

The experiment in which tolerance development under DRL and variable-interval schedules is being compared also provides encouraging information about the generality of data gathered from squirrel monkeys. The effects of Δ^9-THC on the performance under the DRL schedule are similar to those reported by other investigators (Ferraro and Grisham, 1972; Manning, 1973)

who have used other species (chimpanzees and rhesus monkeys). This implies that squirrel monkeys are not peculiar with respect to their reaction to the drug, and also that the drug vehicle and route of administration do not produce atypical effects.

Also of interest in the experiment comparing DRL and variable-interval schedule performance is the fact that in this experiment tolerance did develop to a much greater degree, and more rapidly under the DRL schedule, the schedule in which there was a greater reduction in frequency of food presentation. Taken together with the results of experiment comparing variable-ratio and variable-interval schedule performance, the results of these experiments suggest that there may be a complex interaction between baseline response rates, drug-produced "loss" and tolerance development. As the project continues, hopefully we will be able to analyze and understand this interaction.

A final point of interest lies in the doses of Δ^{c}-THC used under the different procedures. In the experiment comparing performance under DRL and variable-interval schedules a dose of 0.25 mg/kg produced profound behavioral effects, yet in the experiment examining a complex sequence of responses 2.0 mg/kg of the drug was required to observe any effect at all in one monkey. Whether these differences are due to the differences in behavioral procedure or to some other factor remains to be determined.

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